

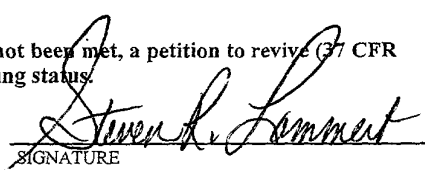
Express Mail No.: EL230257915US

Mailed: 3/ May 2001

JC17 Rec'd PCT/PTO 31 MAY 2001

PCT

FORM PTO-1390 (REV. 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER <b>3220-68450</b>
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 CFR 1.5 Unknown <b>09/857307</b>
INTERNATIONAL APPLICATION NO. <b>PCT/US99/28300</b>	INTERNATIONAL FILING DATE <b>01 December 1999</b>	PRIORITY DATE CLAIMED <b>01 December 1998</b>
TITLE OF INVENTION <b>METHOD FOR VOCAL CORD RECONSTRUCTION</b>		
APPLICANT(S) FOR DO/EO/US <b>BADYLAK, Stephen F.; SPIEVACK, Alan R.</b>		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). <b>Two counterpart executed Declarations with 2 sheets each</b> 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).		
Items 11 to 20 below concern document(s) or information included:		
11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. 14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information: a. <b>Copy of Form PCT/IB/306 (1 sheet)</b> b. <b>Copies of the PCT International Search Report and each reference cited therein</b> c. <b>Copies of the PCT International Preliminary Examination Report and two references cited therein</b>		

U.S. APPLICATION NO (if known, see 37 CFR 1.5) <b>Unknown</b>		INTERNATIONAL APPLICATION NO <b>PCT/US99/28300</b>		ATTORNEY'S DOCKET NUMBER <b>3220-68450</b>	
21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1000.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00 <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>CALCULATIONS PTO USE ONLY</b>	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$ -0-	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	11 -20 =	-0-	x \$18.00	\$ -0-	
Independent claims	3 -3 =	-0-	x \$80.00	\$ -0-	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00	\$ -0-	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 100.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$ -0-	
<b>SUBTOTAL =</b>				\$ 100.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$ -0-	
<b>TOTAL NATIONAL FEE =</b>				\$ 100.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$ -0-	
<b>TOTAL FEES ENCLOSED =</b>				\$ 100.00	
				Amount to be refunded: \$	
				charged: \$	
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>100.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>10-0435</u> A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. <b>Credit card information should not be included on this form.</b> Provide credit card information and authorization on PTO-2038.					
<b>NOTE:</b> Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: <b>LAMMERT, Steven R.</b> <b>BARNES &amp; THORNBURG</b> <b>11 South Meridian Street</b> <b>Indianapolis, IN 46204</b> <b>US</b>					
				 SIGNATURE	
				<b>Steven R. Lammert</b> NAME	
				<b>27653</b> REGISTRATION NUMBER	

09/857307

Express Mail No.: EL230257915US

Mailed: 3/ May 2001 (3/.05.01)

BARNES&THORNBURG

JC05 Rec'd PCT/PTO 31 MAY 2001

11 South Meridian Street  
Indianapolis, Indiana 46204  
(317) 236-1313

PATENT APPLICATION

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

Group: Unknown }  
Attorney }  
Docket: 3220-68450 }  
Applicant: BADYLAK, Steven F.; SPIEVACK, }  
Alan R. }  
Invention: METHOD FOR VOCAL CORD }  
RECONSTRUCTION }  
U.S. Serial No: Unknown }  
International Serial No: PCT/US99/28300 }  
International Filing Date: 01 December 1999 }  
(01.12.99) }  
Earliest Priority Date: 01 December 1998 }  
(01.12.98) }  
Examiner: Unknown }

FIRST PRELIMINARY AMENDMENT

Attention: DO/EO/US  
Box PCT  
Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Preliminary to the examination of the above-identified national patent application submitted herewith, applicants respectfully request entry of the following amendments.

In the Description

After the title, please insert the following paragraph:

Cross-References to Related Applications

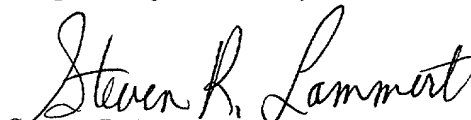
This application is a U.S. national application of international application serial No. PCT/US99/28300 filed December 1, 1999, which claims priority to U.S. provisional applications serial Nos. 60/110,401 and 60/110,465 filed December 1, 1998.

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REMARKS

This Preliminary Amendment is being submitted to indicate the relationship of the subject U.S. national application to previously filed applications as required under 37 C.F.R. 1.78. With the entry of the foregoing amendments, the application is believed to be in condition for examination and allowance. Consideration of the claims, leading to their allowance and passage of the application to issuance, is respectfully requested.

Respectfully submitted,



Steven R. Lammert,  
Atty. Reg. No. 27653  
Attorney for Applicants

SRL/mje/383693  
Indianapolis, Indiana 46204  
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Mailed: 16 August 2001 (16.08.01)

Rec'd PCT/PTO 16 AUG 2001 #3

BARNES&THORNBURG

09/857307

11 South Meridian Street  
Indianapolis, Indiana 46204  
(317) 236-1313

PATENT APPLICATION

*IN THE UNITED STATES PATENT AND TRADEMARK OFFICE*

Group: Unknown }  
Attorney }  
Docket: 3220-68450 }  
Applicant: BADYLAK, Steven F.; SPIEVACK, }  
Alan R. }  
Invention: METHOD FOR VOCAL CORD }  
RECONSTRUCTION }  
U.S. Serial No: 09/857,307 }  
International Serial No: PCT/US99/28300 }  
International Filing Date: 01 December 1999 }  
(01.12.99) }  
Earliest Priority Date: 01 December 1998 }  
(01.12.98) }  
Examiner: Unknown }

RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS UNDER  
35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED  
OFFICE (DO/EO/US)

Attention: DO/EO/US  
Box PCT  
Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

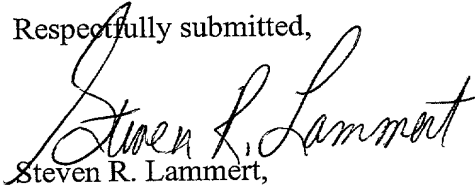
In response to the Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US) and the attached Notification of a Defective Oath or Declaration mailed 05 July 2001 (05.07.01), applicants submit herewith:

1. an original counterpart Declaration and Power of Attorney--Patent Application signed by Alan R. --SPIEVACK-- to replace the counterpart Declaration containing a typographical error in the printed name of the second inventor and signed by Alan R. SPIEVACK on 17 December 1999 (17.12.99) and transmitted to the DO/EO/US on 31 May 2001 (31.05.01);
2. copies of Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US) and Notification of a Defective Oath or Declaration; and
3. Check No. 302764 in the amount of \$130.00 for the surcharge for furnishing a correct counterpart executed oath or declaration later than 30 months from the earliest claimed priority date.

The name of the second inventor Alan R. SPIEVACK on the signed counterpart Declaration now matches and is spelled the same on the Declaration and on the International application.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 10-0435. A duplicate of this Response is enclosed.

Respectfully submitted,



Steven R. Lammert,  
Atty. Reg. No. 27653  
Attorney for Applicants

Attachments: Original Executed Counterpart Declaration and Power of Attorney--  
Patent Application from Alan R. SPIEVACK  
Copies of Notification of Missing Requirements Under 35 U.S.C. 371 in the  
United States Designated/Elected Office (DO/EO/US) and Notification of a  
Defective Oath or Declaration  
Check in the Amount of \$130.00 for Surcharge  
Copy of Response to Notification of Missing Requirements

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## METHOD FOR VOCAL CORD RECONSTRUCTION

### Field of the Invention

The present invention relates to a tissue graft and method for repairing  
5 damaged or diseased head and neck soft tissues. More particularly, this invention is directed to a method for promoting growth of endogenous vocal cord tissue to repair damaged or diseased vocal cords.

### Background and Summary of the Invention

10 There is a significant need for suitable scaffold materials in reconstructive surgery of the head and neck region. Congenital and acquired deformations of structures such as larynx, soft and hard palate, nasal, auricular, and facial bones are common, and biomaterials available for surgical repair of these objects are limited. Contracture, infection, and poor integration into the surrounding tissues are frequent problems with  
15 such materials. Clearly a tissue graft material is desired which is non-immunogenic, is not subject to gross shrinkage after implantation, and promotes the growth of endogenous vocal cord, larynx, soft and hard palate, nasal, and auricular tissues.

The naturally-occurring extracellular matrix (ECM) of the small intestinal submucosa, as well as other vertebrate sources of submucosa, has been shown to serve as  
20 a resorbable scaffold for numerous body systems. Surprisingly, it too has been found that basement membranes (stroma) prepared from liver tissue of warm-blooded vertebrates (by removing cellular components of the liver tissue) exhibit mechanical and biotropic properties suitable for use as a tissue graft material. The present invention is directed to the use of vertebrate submucosa matrices and basement membranes as tissue grafts for  
25 replacing damaged or diseased portions of head and neck soft tissue and promoting the remodeling and regeneration of the tissue graft with endogenous tissues. The submucosa matrices used in accordance with the present invention comprises highly conserved collagens, glycoproteins, proteoglycans, and glycosaminoglycans in their natural configuration and natural concentration. Vertebrate submucosa is a relatively acellular  
30 collagen-based matrix that can be isolated from animal tissues, including particularly intestinal tissue harvested from animals raised for meat production. The isolated



submucosa can be used to prepare a resorbable tissue graft construct for inducing the repair of endogenous tissues.

The basement membrane graft compositions of the present invention comprise the basement membrane of organ tissue of a warm-blooded vertebrate, for example, liver tissue, substantially free, preferably devoid, of all cells (e.g., hepatocytes and bile ductal cells) of said warm-blooded vertebrate. The liver basement membrane can be implanted, or fluidized and injected, into a vertebrate host to contact damaged or defective vocal cord, larynx, soft and hard palate nasal and auricular tissues and induce the repair or replacement of said tissues *in vivo*.

It is known that compositions comprising the tunica submucosa and the basilar portions of the tunica mucosa of the intestine of warm-blooded vertebrates can be used as tissue graft materials in sheet form. See U.S. Patent No. 4,902,508. The compositions described and claimed in that patent are characterized by excellent mechanical properties, including high compliance, a high burst pressure point, and an effective porosity index which allows such compositions to be used beneficially for vascular graft constructs. The graft materials disclosed in that patent are also useful in tendon, ligament and other connective tissue replacement applications. Furthermore, intestinal submucosa has been used as a scaffold for regenerating other tissues including urinary bladder and dura mater. When used in such applications the preferred graft constructs appear to serve as a matrix for the regrowth of the tissues replaced by the graft constructs. Vertebrate submucosa is a plentiful by-product of commercial meat production operations and is thus a low cost tissue graft material, especially when the submucosa is used in its native sheet configuration. Intestinal submucosa has undergone extensive immunologic testing in over 600 cross-species implants and has never been shown to elucidate a rejection reaction.

Furthermore, it is known that intestinal submucosa can be fluidized by comminution and/or protease digestion, without loss of its apparent biotropic properties, for use in less invasive methods of administration (e.g., injection or topical) to host tissues in need of repair. See U.S. Patent No. 5,275,826 the disclosure of which is expressly incorporated herein. Fluidized comminuted intestinal tissue comprising tunica submucosa has previously been successfully used to repair and functionally augment damaged tissues including, for example, urinary bladder sphincter. Common events to tissue remodeling

include widespread and rapid neovascularization, proliferation of granulation mesenchymal cells, biodegradation of implanted submucosa, and lack of immune rejection.

The present invention is directed to the use of vertebrate-derived submucosa or basement membrane matrices as a graft for the regeneration and repair of head and neck soft tissues including the larynx, vocal cords, soft and hard palate, attached gingiva, nasal and auricular tissues. Such vertebrate extracellular matrices are inexpensive, nonimmunogenic materials that induce host tissue proliferation, remodeling and regeneration upon implantation. In accordance with one embodiment of the present invention tissue graft constructs comprising submucosa or basement membrane of a warm-blooded vertebrate have been found to promote the growth of endogenous vocal cord tissues including the oral mucosal epithelium, connective tissue and skeletal muscle. The graft constructs of the present invention can be used to repair or reconstruct structures damaged by cancer or resulting from congenital defects. The method comprises replacing the damaged or diseased tissues with the construct which acts as a scaffold for endogenous cell growth and replacement of the graft construct. The scaffold is typically entirely replaced by endogenous tissues in about three to six weeks.

#### Detailed Description of the Invention

There is provided in accordance with the present invention a method and composition for repairing damaged or diseased head and neck soft tissues including the vocal cord, larynx, soft and hard palate, attached gingiva, nasal and auricular tissues. The extracellular matrix graft compositions function as a biotropic/biodegradable scaffold that induces endogenous tissues to invade and replace the graft material with endogenous tissue. After implantation, the constructs are eventually remodeled by the host with tissues having a stratification of cell layers similar to that found in normal endogenous tissues.

One tissue graft construct used in accordance with the present invention is derived from vertebrate submucosa and comprises naturally associated extracellular matrix proteins, glycoproteins and other factors. Suitable submucosa comprises the tunica submucosa delaminated from the tunica muscularis and at least the luminal portion of the tunica mucosa. Preferably, the submucosa comprises intestinal submucosa of a

5 warm-blooded vertebrate, and one particularly preferred source of the submucosa is the small intestine of warm-blooded vertebrates. In accordance with one embodiment of the present invention the submucosa is intestinal submucosa comprising the tunica submucosa and basilar portions of the tunica mucosa including the lamina muscularis mucosa and the stratum compactum which layers are known to vary in thickness and in definition dependent on the source vertebrate species. Submucosa can also be prepared from other organs of vertebrate species, for example, from the urogenital system, including the urinary bladder (see U.S. Patent Nos. 5,554,389), and other portions of the digestive tract including the stomach (see published PCT application no. WO98/25636). The disclosures  
10 of U.S. Patent Nos. 5,554,389 and published PCT application no. WO98/25636 are expressly incorporated herein.

The preparation of vertebrate submucosa for use in accordance with this invention is described in U.S. Patent Nos. 4,902,508 and 5,554,389. To summarize, submucosa is prepared from vertebrate intestine (or other organ source), preferably  
15 harvested from porcine, ovine or bovine species, but not excluding other species, by subjecting the intestinal tissue to abrasion using a longitudinal wiping motion to remove the outer layers, comprising smooth muscle tissues, and the innermost layer, *i.e.*, at least the luminal portion of the tunica mucosa. The submucosa is rinsed with saline and optionally sterilized; it can be stored in a hydrated or dehydrated state. Lyophilized or air  
20 dried vertebrate submucosa can be rehydrated and used in accordance with this invention without significant loss of its cell proliferative activity. Native submucosa as a starting material is a relatively acellular collagenous matrix and the process of preparing intestinal submucosa for use as the collagenous matrix component of the present invention produces a collagenous matrix devoid of intact cells. Accordingly the submucosa  
25 collagenous matrix prepared in accordance with the present invention is acellular.

It is known that compositions comprising the tunica submucosa of the intestine of warm-blooded vertebrates can be used advantageously as tissue graft materials. See U.S. Patent Nos. 4,902,508 and 5,281,422, the disclosures of which are expressly incorporated herein by reference. The tissue graft compositions described in  
30 those patents are used beneficially for vascular graft and connective tissue graft constructs. When used in such applications the graft constructs appear not only to serve as a matrix for the regrowth of the tissues replaced by the graft constructs, but also

promote or induce such regrowth of endogenous tissue. Common events to this remodeling process include widespread and rapid neovascularization, proliferation of granulation mesenchymal cells, biodegradation/resorption of implanted submucosa, and lack of immune rejection.

5                   It is also known that intestinal submucosa can be fluidized by comminuting and/or enzymatic digestion, without loss of its apparent biotropic properties, for use in less invasive methods of administration (e.g., by injection or topical application) to host tissues in need of repair. See U.S. Patent No. 5,275,826, the disclosure of which is expressly incorporated herein by reference.

10                   In another embodiment of the invention the tissue graft composition comprises liver basement membrane prepared by separating same from the natively associated cellular components of liver tissue of a warm-blooded vertebrate. The preparative techniques described below provide an extracellular matrix composition consisting essentially of liver basement membrane substantially free of any cellular  
15 components. These compositions are referred to herein generically as liver basement membrane(s) (LBM). Other organ tissue sources of basement membrane for use in accordance with this invention include spleen, lymph nodes, salivary glands, prostate, pancreas and other secreting glands.

                  Basement membrane for preparation of the graft compositions used in  
20 accordance with this invention is typically prepared from liver tissue harvested from animals raised for meat production, including, for example, pigs, cattle and sheep or other warm-blooded vertebrates. Thus, there is an inexpensive commercial source of liver tissue for use in preparation of the basement membrane derived tissue graft compositions for use in accordance with the present invention. In one embodiment, a composition  
25 comprising liver basement membranes is prepared from liver tissue of a warm-blooded vertebrate. This composition is useful in accordance with this invention as a non-immunogenic tissue graft capable of inducing endogenous tissue growth when implanted in warm-blooded vertebrates. In one embodiment, the composition comprises an extracellular matrix consisting essentially of liver basement membrane devoid of  
30 endogenous cells associated with the source vertebrate liver tissue used to prepared the composition.

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The preparation of liver basement membrane from liver tissue of a warm-blooded vertebrate is carried out by removing the cellular components from liver tissue. Ideally the process is carried out to separate the cells from the basement membranes without damaging, or at least minimizing disruption or damage to, the basement

5 membrane tissue. Removal of the cellular components from the liver extracellular matrix allows the preparation of a graft composition that is non-immunogenic, and thus does not induce a host immune response when the graft composition is implanted into a host. In general, the method for preparing a tissue graft composition from warm-blooded

10 vertebrate liver tissue comprises the steps of treating the liver tissue with a cell dissociation solution for a period of time sufficient to release the cellular components of the liver tissue from the extracellular components without substantial disruption of the extracellular components, and separating the cellular components from said extracellular components. Typically the cell dissociation solution comprises a chaotropic agent or an enzyme or both.

15 The first step in preparing liver basement membrane for use in accordance with one embodiment of the present invention comprises slicing a segment of liver tissue into pieces (*e.g.*, strips or sheets) to increase the surface area-to-volume ratio of the liver tissue. In one embodiment the liver tissue is sliced into a series of sheets each having a thickness of about 0.05 to about 1.5 mm, more particularly, about 50 to about 500

20 microns, and more preferably about 250 to about 300 microns. Freshly harvested liver tissue can be sliced using a standard meat slicer, or the tissue can be frozen and sliced with a cryomicrotome. The thin pieces of liver tissue are then treated with a solution that releases component liver cells from the associated extracellular basement membrane matrix.

25 The liver tissue can be also treated with a solution comprising an enzyme, for example, a protease, such as trypsin or pepsin. Because of the collagenous structure of the liver basement membrane and the desire to minimize degradation of the membrane structure during cell dissociation, collagen specific enzyme activity should be minimized in the enzyme solutions used in the cell-dissociation step. In addition, the liver tissue is

30 typically also treated with a calcium chelating agent or chaotropic agent such as a mild detergent such as Triton 100. Thus, in one embodiment of this invention liver tissue is treated by suspending slices or strips of the tissue in a cell-dissociation solution containing

enzyme(s) and chaotropic agent(s). However, the cell dissociation step can also be conducted using a calcium chelating agent or chaotropic agent in the absence of an enzymatic treatment of the tissue.

In preparative method the cell-dissociation step is carried out by  
5 suspending liver tissue slices in an agitated solution containing about 0.05 to about 2%, more typically about 0.1 to about 1% by weight protease, optionally containing a chaotropic agent or a calcium chelating agent in an amount effective to optimize release and separation of cells from the basement membrane without substantial degradation of the membrane matrix.

10 After contacting the liver tissue with the cell-dissociation solution for a time sufficient to release all cells from the matrix, the resulting liver basement membrane is rinsed one or more times with saline and optionally stored in a frozen hydrated state or a partially dehydrated state until used as described below. The cell-dissociation step may require several treatments with the cell-dissociation solution to release substantially all  
15 cells from the basement membrane. In one embodiment liver tissue is treated with a protease solution to remove the component cells, and the resulting extracellular matrix material (basement membrane) is further treated to remove or inhibit any residual enzyme activity. For example, the resulting basement membrane can be heated or treated with one or more protease inhibitors.

20 Liver basement membrane for use in carrying out this invention can be fluidized (converted to an injectable or powder form) in a manner similar to the preparation of fluidized intestinal submucosa, as described in U.S. Patent No. 5,275,826 the disclosure of which is expressly incorporated herein by reference.

In accordance with one embodiment of the present invention a multi-  
25 layered submucosa or basement membrane construct is formed from multiple sheets/strips of submucosa and/or basement membrane. The method of forming the multi-layered construct comprises the steps of overlapping multiple sheets of submucosa and/or basement membrane and adhering the layers to each other. The individual layers can be fix to one another using standard techniques know to those skilled in the art and including  
30 the use of sutures, staples and biocompatible adhesives such as collagen binder pastes. In one embodiment the layers are fused together by compressing the overlapped regions under dehydrating conditions, optionally with the addition of heat.

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The individual layers forming the multi-layered construct can be prepared from sheets of submucosa and/or basement membrane, wherein each sheet is cut to the same dimensions. Alternatively each sheet of the multilayered construct may be cut to have different dimensions, and in one embodiment the sheets comprising the multi-layered  
5 construct may have the same width and length but may differ in thickness. Typically the sheets of basement membrane will be cut to have a thickness of about 0.05 mm to about 1.5 mm, and more preferably about 0.2 to about 0.5 mm.

In one embodiment of the present invention, a first strip of submucosa or basement membrane can be partially overlapped with a second strip of submucosa or  
10 basement membrane and the two strips adhered to one another to form a large area, graft construct as described in US Patent No. 5,711,969, the disclosure of which is expressly incorporated herein. The process of forming large area graft sheets involves cutting strips of submucosa and overlapping at least a portion of each strip with a portion of an adjacent strip. The overlapped regions are then adhered to one another using techniques  
15 known to those skilled in the art. Alternatively, consecutive layers of extracellular matrix material (submucosa and/or basement membrane) can be layered on top of one another so that each layer is entirely covered by the second layer, thus generating a multi-layered construct uniform in thickness throughout the graft construct. In one embodiment the multi-layered constructs are perforated to allow fluids to readily pass through the graft  
20 construct and prevent pockets of fluids from accumulating between the layers. The formation of perforated multilayered constructs is described in US Patent No. 5,755,791, the disclosure of which is expressly incorporated herein.

In one embodiment, the overlapped portions are compressed under dehydrating conditions to fuse the overlapped portions to one another and form a large  
25 sheet. In one preferred embodiment, a multi-layered graft construct is prepared without the use of adhesives or chemical pretreatments by compressing at least the overlapped portions of extracellular matrix under conditions that allow dehydration of the material concurrent with the compression of the tissue. To promote dehydration of the compressed material, at least one of the two surfaces compressing the tissue is water  
30 permeable. Dehydration can optionally be further enhanced by applying blotting material, heating the material or blowing air across the exterior of the two compressing surfaces.

In one embodiment the method of forming the multi-layered construct comprises layering the strips onto a permeable surface and using a second optionally permeable surface to compress the overlapped portions between the two surfaces. In one embodiment, strips are organized on a mesh in one direction with at least a portion of one strip overlapping with at least a portion of another strip. Once the mesh is covered with one layer of extracellular matrix material a second layer is applied on top of the first layer but at a different angle relative to the first layer. Additional layers can be added to obtain a graft construct having a desired strength or thickness.

After all the strips are placed on the mesh, another mesh is placed on top of the layers and the "mesh-tissue layers-mesh" sandwich is compressed with a load and dried. This process produces a dried large area construct that can be peeled off the mesh.

In one embodiment the graft construct is formed from two or more strips of extracellular matrix material pressed together and dried through the use of vacuum bagging. In that method submucosa or basement membrane is laid out between two perforated, preferably stainless steel, plates. The plates are shaped to define the desired shape, e.g. two concentric cylinders are used to form a multilayered tubular construct. The material is optionally placed on a surface and covered with blotting material to soak up water, and a breather blanket to allow air flow. The resulting "sandwich" of pressure plates and matrix material is then sealed into a nylon bag that has a vacuum port. A vacuum is applied to pull air out of the vacuum bag and the resulting drop in atmospheric pressure compresses the plates against the matrix material and simultaneously, at least partially, dehydrates the material. After 4 to 24 hours of applying a vacuum, the produced sheet is still moist and very flexible. No seams from the layering are visible and the strength of a prototype 8-thickness sheet as determined by ball burst test is approximately 80 pounds. This general procedure can also be used to shape single tissue strips for use in this invention, if "shaping" of such single layer tissue constructs is determined to be necessary or appropriate for particular surgical application.

In one embodiment, during formation of the large area sheets of tissue, pressure is applied to the overlapped portions under dehydrating conditions by compressing the overlapped tissue segments between two surfaces. The two surfaces can be formed from a variety of materials and in any shape, depending on the desired form and specification of the targeted graft construct. Typically the two surfaces are formed as



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In one embodiment the submucosa is stretched using 50% of the predicted ultimate load. The "ultimate load" is the maximum load that can be applied to the submucosa without resulting in failure of the tissue (i.e. the break point of the tissue). Ultimate load can be predicted for a given strip of submucosa based on the source and thickness of the material. Accordingly, one method of conditioning the tissue by stretching involves application of 50% of the predicted ultimate load to the submucosa for three to ten cycles. Each cycle consists of applying a load to the graft material for five seconds, followed by a ten second relaxation phase. The resulting conditioned submucosa has a strain of less than 30%, more typically a strain from about 20% to about 28%. In one preferred embodiment conditioned the submucosa has a strain of no more than 20%. The term strain as used herein refers to the maximum amount of tissue elongation before failure of the tissue, when the tissue is stretched under an applied load. It is expressed as a percentage of the length of the tissue before loading. The conditioned submucosal strips can be used to form a graft construct of the present invention or alternatively the graft construct can be conditioned after its formation. For the multi-layered constructs the submucosa can be stretched prior to the formation of the graft construct, during the formation of the construct, or the submucosa can be stretched after formation of the multi-layered construct.

The graft compositions of the present invention can be sterilized using conventional sterilization techniques including glutaraldehyde tanning, formaldehyde tanning at acidic pH, ethylene oxide treatment, propylene oxide treatment, gas plasma sterilization, gamma radiation, electron beam and peracetic acid sterilization. Sterilization techniques which do not adversely affect the mechanical strength, structure, and biotrophic properties of the graft constructs are preferred. For instance, strong gamma radiation may cause loss of strength of the sheets. Preferred sterilization techniques include exposing the graft to peracetic acid, 1-4 Mrads gamma irradiation (more preferably 1-2.5 Mrads of gamma irradiation) or gas plasma sterilization; peracetic acid sterilization is the most preferred sterilization method. Typically, the graft construct is subjected to two or more sterilization processes. After sterilization, for example by chemical treatment, the tissue graft construct may be wrapped in a plastic or foil wrap and sterilized again using electron beam or gamma irradiation sterilization techniques.

There is provided in accordance with the present invention a method and composition for repairing damaged or diseased head and neck soft tissues including the vocal cord, larynx, soft and hard palate, attached gingiva, nasal and auricular tissues. The above described graft compositions function as a biotropic/biodegradable scaffold that induces endogenous tissues to invade and replace the graft material with endogenous tissue. Advantageously the graft constructs induce the proliferation of endogenous cells to form native tissues of the native structure, including an epithelial cell layer, connective tissue and functional muscle.

In accordance with one embodiment of the present invention, vertebrate submucosa or basement membrane material is used as a tissue graft for reconstructing damaged or diseased larynx and vocal cord tissues. In one embodiment a damaged or diseased section of the vocal cord, or even the entire vocal cord, is removed and replaced with a tissue graft construct as described above. The tissue graft induces the growth of endogenous vocal cord tissues, including oral mucosal epithelial cells, and functional skeletal muscles, and thus promotes the repair of the damaged or diseased tissues. The method of repair comprises the steps of surgically removing the damaged or diseased portion and replacing the removed portion with a tissue graft construct comprising submucosa or basement membrane of a warm-blooded vertebrate. Controls indicate that in the absence of the present graft material, severed vocal cords form scar tissue at the wound site and fail to regenerate the severed vocal cord.

In one embodiment submucosa used for the repair of head and neck soft tissues is isolated from intestinal tissue and comprises the tunica submucosa delaminated from both the tunica muscularis and at least the luminal portion of the tunica mucosa. Alternatively, the submucosa can be prepared from urinary bladder or stomach tissues. In accordance with one embodiment the tissue graft construct comprises multiple layers of vertebrate submucosa comprising 2-12 layers of submucosa, more preferably 4-6 layers. The multi-layered construct in one embodiment comprises partially overlapped strips of submucosa and more preferably the tissue graft construct is formed as a multilayered homolaminate (i.e. having the same number of layers throughout the graft) construct. Basement membrane material can be used similarly alone or in combination with submucosa tissue.

In accordance with one embodiment of the present invention, there is provided a method for reconstructing diseased or damaged vocal cord tissues. The method comprises the steps of surgically removing the damaged or diseased vocal cord tissues and replacing the removed tissues with a tissue graft construct comprising an  
5 extracellular matrix of a warm-blooded vertebrate. In one embodiment the entire vocal cord is removed and replaced with submucosa tissue or basement membrane tissue or some combination thereof. The graft construct serves as a scaffold for inducing the proliferation and repair of the vertebrate vocal cords. The graft is remodelled within about three to six weeks forming functional skeletal muscle, an oral mucosal epithelial  
10 layer and supporting connective tissue. The tissue graft constructs can be implanted into a vertebrate host species to repair a damaged, diseased or otherwise functionally compromised vocal cord. The xenogeneic materials do not elicit any adverse immune response or adverse inflammatory reaction. The scaffolds appear to be rapidly resorbed and replaced by varying amounts of host connective tissues without shrinkage of the graft  
15 area or formation of "scar" tissue.

In one embodiment the defective portion of the larynx or vocal cord is surgically removed and replaced with a tissue graft construct comprising submucosa of a warm-blooded vertebrate. Where the submucosa is of intestinal origin it is preferred that the luminal side of the intestinal submucosa is directed toward the larynx lumen. Large  
20 portions of the larynx can be removed and replaced with the tissue grafts of the present invention. After implantation, the constructs are eventually remodelled by the host with functional larynx tissues having a stratification of cell layers similar to that found in the normal larynx wall.

It is anticipated that vertebrate submucosa and/or basement membrane is  
25 capable of inducing host tissue proliferation, remodeling and regeneration of appropriate tissue structures upon implantation in a number of microenvironments *in vivo* (e.g. soft tissues of the head and neck, including the larynx, vocal cords, soft and hard palate, attached gingiva, nasal and auricular tissues). In one embodiment of the present invention the tissue replacement capabilities of graft compositions comprising vertebrate submucosa  
30 or basement membrane of warm-blooded vertebrates are further enhanced or expanded by seeding the tissue with various cell types, prior to implantation. For example, a submucosa construct may be seeded with mesenchymal cells (stem cells) initially for

expansion of the cell population and thereafter for implantation into a host. In accordance with one embodiment the constructs are seeded with epithelial cells before implantation of the graft construct. In accordance with another embodiment epithelial cells are first cultured on one side of the graft construct and then muscle cells are cultured on the opposite side of the graft construct before the graft is implanted.

### Example 1

#### Preparation of intestinal submucosa

Small intestine submucosa was prepared in accordance with the procedures described in U.S. Patent No. 4,902,508. Briefly, sections of porcine jejunum were harvested within ten minutes of euthanasia and immediately placed in 0.9% saline solution. These sections were cut into 10 to 20 cm lengths and the mesenteric tissues were removed from the segment of the small intestine. The small intestine was exerted (inside out) and the tunica mucosa mechanically removed. The small intestinal segment was exerted again (i.e. the stratum compactum on the luminal side, as in the original orientation) and the serosa and tunica muscularis were removed from the outer surface. The tissue was rinsed in saline and placed in a 10% neomycin sulfate solution until used as a graft material. Storage time for the graft material ranged from 2 weeks to 3 months. It should be noted that preparation of submucosa is a mechanical process similar to that of sausage casing and involves no enzymatic reaction steps.

### Example 2

#### Surgical Repair of vocal cords

**Materials and Methods:** Seven healthy adult female mongrel dogs were subjected to bilateral resection of the vocal folds. One side was repaired with a single thickness sheet of either intestinal submucosa or urinary submucosa both of which are resorbable naturally-occurring scaffolds. The contralateral side in each dog was left unfilled as a control. The dogs were evaluated at time points ranging from three weeks to several months.

**Results:** At three weeks, there was significant remodeling along the framework of the resorbable scaffolds. Deposition of new extracellular matrix, an abundant vascular

component, and a dense infiltration of mononuclear cells existed within the space occupied by the original graft construct. At three weeks, none of the graft constructs could be identified with either routine H&E staining or Masson's Trichrome staining. There was a subtotal epithelialization of the surface of each of these grafts. The

5 contralateral (control) side showed scar tissue formation partially filling the defect. Macroscopic and microscopic results of the longer surviving dogs are in preparation.

### Example 3

#### Preparation of Liver Basement Membrane

##### 2 mM EDTA Chaotropic Solution Used In The Experiment

10	140mM	NaCl
	5mM	KCl
	0.8mM	MgSO <sub>4</sub>
	0.4mM	KH <sub>2</sub> HPO <sub>4</sub>
	2mM	EDTA
15	25mM	NaHCO <sub>3</sub>

#### Procedure:

##### *Preparation of liver slices:*

Liver frozen in -70°C was sliced with a cryomicrotome to a thickness of

20 about 50µM. The slices of liver tissue were then subjected to enzymatic treatment (trypsin) with a chaotropic solution (samples 1 and 2), with enzyme alone (samples 3 and 4), or with a chaotropic solution alone (sample 5), as indicated below.

Sample #	Treatment
25	1) 0.05% Trypsin in 2mM EDTA solution
	2) 0.1% Trypsin in 2mM EDTA solution
	3) 0.05% Trypsin in 2mM PBS
	4) 0.1% Trypsin in 2mM PBS
	5) 2mM EDTA solution

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Liver slices were placed in five 50ml tubes, each of which contained 25mL of a different buffered enzyme treatment solution. The liver tissue was incubated at 37°C

in water bath with gentle shaking for 1 hour. The liver slices were washed twice with PBS with agitation/shaking for 1 hour at room temperature. The above enzymatic treatment steps were repeated three times.

The wash buffers were collected and spin them down in 2000rpm for 10 min. The pellet was suspended and an equal amount of trypan blue was added to identify any remaining cells. The material was checked for presence of cells under microscope.

#### Example 4

##### Mechanical Properties of Isolated Liver Basement Membrane

Porosity of a graft material is typically measured in terms of ml of water passed per  $\text{cm}^2\text{min}^{-1}$  at a pressure of 120 mm Hg. The average "porosity index" established for two separate specimens of LBM was 1162. The suture retention strength of LBM is approximately 68 grams. The material appears to be anisotropic, with the suture strength being approximately the same in all directions.

#### Example 5

##### Surgical Repair of vocal cords

**Materials and Methods:** Seven healthy adult female mongrel dogs were subjected to bilateral resection of the vocal folds. One side was repaired with a single thickness sheet of LBM which is a resorbable naturally-occurring scaffold. The contralateral side in each dog was left unfilled as a control. The dogs were evaluated at time points ranging from three weeks to several months.

**Results:** At three weeks, there was significant remodeling along the framework of the resorbable scaffolds. Deposition of new extracellular matrix, an abundant vascular component, and a dense infiltration of mononuclear cells existed within the space occupied by the original graft construct. At three weeks, none of the graft constructs could be identified with either routine H&E staining or Masson's Trichrome staining. There was a subtotal epithelialization of the surface of each of these grafts. The contralateral (control) side showed scar tissue formation partially filling the defect. Macroscopic and microscopic results of the longer surviving dogs are in preparation.

## CLAIMS:

1. A method for the repair or replacement of vocal cord tissues comprising the steps of:
- 5 removing the a damaged or diseased portion of a vocal cord, and  
replacing the removed portion of a vocal cord with a graft construct comprising vertebrate submucosa or basement membrane.
2. The method of claim 1 wherein the graft comprises submucosa and the submucosa is selected from the group consisting of intestinal submucosa, urinary  
10 bladder submucosa, and stomach submucosa.
3. The method of claim 2 wherein the submucosa is intestinal submucosa and comprises the tunica submucosa delaminated from the tunica muscularis and the luminal portion of the tunica mucosa.
4. The method of claim 1 wherein the graft construct comprises  
15 vertebrate basement membrane.
5. The method of claim 1 wherein the graft construct comprises 2-12 layers of submucosa.
6. The method of claim 1 wherein the graft construct comprises 4-6 layers of submucosa.
- 20 7. The method of claim 5 wherein the graft construct is formed as a multilayered homolaminate.
8. The method of claim 1 wherein the graft construct comprises a single thickness sheet of submucosa.
9. A method for the repair or replacement of damaged or diseased  
25 head and neck soft tissues comprising the steps of  
removing the a damage or diseased portion of the diseased or damaged tissue, and  
replacing the removed portion of tissue with a graft construct comprising vertebrate submucosa or basement membrane.
- 30 10. The method of claim 8 wherein the head and neck soft tissues are selected from the group consisting of vocal cord, larynx, palette, attached gingiva, nasal, and auricular tissues.

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11. The use of vertebrate submucosa or vertebrate basement membrane to manufacture a non-immunogenic tissue graft composition for repairing vocal cords and other soft tissues of the head and neck.

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**METHOD FOR VOCAL CORD RECONSTRUCTION**Abstract of the Disclosure

- 5                   A method for surgical repair of damaged or diseased head and neck tissues is described. In one aspect of the invention tissue graft constructs comprising vertebrate submucosa or vertebrate basement membrane materials are used to repair and promote growth of endogenous vocal cord tissue.

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Attorney Docket No.: 3220-

P-98095.00.US

## DECLARATION AND POWER OF ATTORNEY - PATENT APPLICATION

As a below named inventor, I hereby declare that I believe I am the original, first and sole inventor (*if only one name is listed below*) or an original, first and joint inventor (*if plural names are listed below*) of the subject matter which is claimed and for which a patent is sought in the application entitled:

METHOD FOR VOCAL CORD RECONSTRUCTION

specification of which

(check one)

\_\_\_\_\_ is attached hereto

XX was filed on 01 December 1999 (01.12.99)

as

United States Application Serial No. \_\_\_\_\_

or

PCT International Application No. PCT/US99/

and was amended on \_\_\_\_\_

(if applicable)

I hereby declare that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to herein.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate on which priority is claimed (as listed below) and I have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

(Number)

(Country)

(Day/Month/Year Filed)

Yes

No

(Number)

(Country)

(Day/Month/Year Filed)

Yes

No

I hereby claim benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/110,401

Application Number

01 December 1998 (01.12.98)

Filing Date

60/110,465

Application Number

01 December 1998 (01.12.98)

Filing Date

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(b) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.

Filing Date

Status-patented, pending, abandoned

Application Serial No.

Filing Date

Status-patented, pending, abandoned

I hereby appoint William R. Coffey, Reg. No. 24023; Richard D. Conard, Reg. No. 27321; Steven R. Lammert, Reg. No. 27653; Richard A. Rezek, Reg. No. 30796; Timothy E. Niednagel, Reg. No. 33266; Nancy J. Harrison, Reg. No. 27083; R. Trevor Carter, Reg. No. 40549; Dilip A. Kulkarni, Reg. No. 27510; David B. Quick, Reg. No. 31993; Jill T. Powlick, Reg. No. 42088; Norman J. Hedges, Reg. No. 44151; Arland T. Stein, Reg. No. 28062; William B. Richards, Reg. No. 44301; Kenneth J. Waite, Reg. No. 45189; Thomas S. Reynolds III, Reg. No. 45262; Perry Palan, Reg. No. 26213; Mark M. Newman, Reg. No. 31472; Bobby B. Gillenwater, Reg. No. 31105; Paul B. Hunt, Reg. No. 37154; Michael S. Gzybowski, Reg. No. 32816; Gerard T. Gallagher,

Reg. No. ~~39679~~; Robert D. Null, Reg. No. ~~40746~~; Alice O. Martin, Reg. No. ~~35601~~; and Gregory S. Cooper, Reg. No. ~~40965~~, as attorneys of record with full power of substitution and revocation, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith, and I specify that communications regarding the application be directed to:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Country of Citizenship

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Full Name of Fourth Joint Inventor, if any

Country of Citizenship

Inventor's Signature

Date

Residence and Post Office Address

Additional inventors to be similarly identified on attached sheet.

## DECLARATION AND POWER OF ATTORNEY – PATENT APPLICATION

As a below named inventor, I hereby declare that I believe I am the original, first and sole inventor (*if only one name is listed below*) or an original, first and joint inventor (*if plural names are listed below*) of the subject matter which is claimed and for which a patent is sought in the application entitled:

METHOD FOR VOCAL CORD RECONSTRUCTION, the  
specification of which

(check one) \_\_\_\_\_ is attached hereto

XX was filed on 01 December 1999 (01.12.99) as

United States Application Serial No. \_\_\_\_\_ or

PCT International Application No. PCT/US99/28300

and was amended on \_\_\_\_\_

I hereby declare that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to herein.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate on which priority is claimed (as listed below) and I have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

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(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
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Scott M. Lohnes, Reg. No. 45451; Thomas J. Donovan, Reg. No. 33231; Alice O. Martin, Reg. No. 35601; Grant H. Peters, Reg. No. 35977; Mark A. Hamill, Reg. No. 37145; Michael B. Allen, Reg. No. 37582; and Daniel P. Albers, Reg. No. 44008, as attorneys of record with full power of substitution and revocation, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith, and I specify that communications regarding the application be directed to:

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